IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	10/629,975	Confirmation No. 9513
Applicant	:	James Hunter Boone	
Filed	:	07/30/2003	
Title	:	METHOD FOR DIFFERENTIATING IRRITABLE BOWEL SYNDROME FROM INFLAMMATORY BOWEL DISEASE (IBD) AND FOR MONITORING PERSONS WITH IBD USING TOTAL ENDOGENOUS LACTOFERRIN AS A MARKER	
Group Art Unit	:	1641	
Examiner	:	Lisa V. Cook	
Docket No.	:	TLAB.109338	
Customer No.	:	05251	

Submitted VIA EFS WEB– December 12, 2008

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Applicants request review of the rejection in the above-identified application. No amendments are being filed with this request. This request is being filed with a Notice of Appeal. The review is requested for the reasons set forth in the Remarks that begin on page 2 of this paper.

REMARKS

Status of Claims

Claims 1, 2, and 6 are pending herein and have been at least twice rejected. Claims 1, 2, and 6 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,358,939 to Hayes et al. (hereinafter the "Hayes reference"), in view of Sreekant Murthy, PhD (Inflammation Research Association, Newsletter, September & December 1999, Vol. 9, No. 3 & 4, pages 1-14) (hereinafter the "Sreekant Murthy reference"), and further in view of US Patent No. 5,552,292 to Uchida et al. (to "Uchida reference") and Aguila La O et al. (Biotecnologia Aplicada, Julio-Septembre, 2000, Vol. 17, No. 3, pages 177-182, English Abstract) (the "Aguila La O reference").

Claims 1, 2, and 6 also stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the Hayes reference, in view of the Sreekant Murthy reference, and further in view of Sugi et al. (The American Journal of Gastroenterology, Vol. 91, No. 5, 927-934) (hereinafter the "Sugi reference") and the Aguila La O reference.

The following remarks illustrate that the rejections of record are clearly not proper and are without basis. As such, claims 1, 2, and 6 are believed to be in condition for allowance upon review of these remarks, and favorable action is respectfully requested.

Legal and Factual Deficiencies

Title 35 U.S.C. § 103(a) declares, a patent shall not issue when "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." The Supreme Court in Graham v.

John Deere counseled that an obviousness determination is made by identifying: the scope and content of the prior art; the level of ordinary skill in the prior art; the differences between the claimed invention and prior art references; and secondary considerations.[1] To support a finding of obviousness, the initial burden is on the Office to apply the framework outlined in Graham and to provide some articulated reason, suggestion, or motivation, found either in the prior art references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the prior art reference or to combine prior art reference teachings to produce the claimed invention.[2] Recently, the Supreme Court elaborated, at pages 13-14 of the *KSR* opinion, that "it will be necessary for [the Office] to look at interrelated teachings of multiple [prior art references]; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by [one of] ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the [patent application]."[3] Accordingly, in order to establish a *prima facie* case of obviousness, the Office shall provide a "clear articulation of the reason(s) why the claimed invention would have been obvious" based on factual findings upon applying the *Graham* factual inquiries.[4]

Applicants respectfully submit that a *prima facie* case of obviousness has clearly not been established for claims 1, 2, and 6. In particular, the Hayes reference in view of the Sreekant Murthy reference, and in further view of the Uchida reference and the Aguila La O reference fails teach or suggest all the limitations of the rejected claims.

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[1] *Graham v. John Deere Co.*, 383 U.S. 1 (1966).
[2] *See, Application of Bergel,* 292 F. 2d 955, 956-957 (1961).
[3] *KSR v. Teleflex*, No. 04-1350, 127 S.Ct. 1727 (2007).
[4] MPEP § 2143

By way of background, embodiments of the present invention are directed to a method for monitoring a person having inflammatory bowel disease for gastrointestinal inflammation. A first human fecal sample from a person is obtained and the concentration of lactoferrin in the first human fecal sample is determined. The first fecal sample is diluted. The first sample is contacted with immobilized polyclonal antibodies to endogenous lactoferrin to create a first treated sample. The first treated sample is contacted with enzyme-linked polyclonal antibodies to create a first readable sample. The optical density of the first readable sample is determined at 450nm. A purified lactoferrin standard curve is generated and a linear portion of the standard curve is determined. The optical density of the first readable sample is compared to the standard curve to determine a concentration of the first diluted sample and to determine whether the concentration of the first diluted sample is within the linear portion of the standard curve. If the first diluted sample is within the linear portion of the standard curve, the concentration of total endogenous lactoferrin in the first fecal sample is determined.

A second human fecal sample from the same person is obtained at a time after the first sample was obtained, and the concentration of lactoferrin in the second human fecal sample is determined. The lactoferrin concentration of the first fecal sample is compared to the lactoferrin concentration of the second fecal sample for the person to monitor the inflammatory bowel disease activity of the person and determine if the person has had a decrease or increase in gastrointestinal inflammation.

The pending claims include independent claims 1 and 6. Each of the independent claims recites limitations directed to obtaining a first fecal sample from a person and obtaining a second fecal sample from the same person, at a time subsequent to obtaining the first fecal sample, and then comparing the lactoferrin concentration of the first fecal sample with the

lactoferrin concentration of the second fecal sample. The cited references clearly fail to describe the limitations recited by these claims.

The Hayes reference fails to teach or suggest comparing the lactoferrin concentration of a first sample with the lactoferrin concentration of a second sample from the same human to determine if the person has had a decrease or increase in gastrointestinal inflammation. The invention of claim 1 is directed to a method that is sensitive enough to monitor changes in lactoferrin levels at different times in the same human to determine if the person has had a change in gastrointestinal inflammation. This allows a physician to know whether an IBD flare may be imminent before the onset of symptoms or may allow a physician to know whether a treatment, such as a pharmaceutical, has been effective in decreasing gastrointestinal inflammation using a non-invasive method.

By way of contrast, column 23, lines 46-60 of the Hayes reference describes looking at symptoms of IBD, and not lactoferrin concentration, to determine if a calcitriol treated mouse exhibited reduced symptoms of disease as compared to controls. Thus, while the Hayes reference describes that weight, fecal and blood hemoglobin, and fecal lactoferrin of MICE are plotted as a function of time, no comparison is done and only symptoms of IBD are evaluated to determine if mice exhibit reduced symptoms of disease. Symptoms of IBD in the Hayes reference are defined as "abdominal pain, diarrhea, rectal bleeding, weight loss, fever, loss of appetite, and other more serious complications, such as dehydration, anemia and malnutrition." *See* Hayes reference, col. 3, ll. 15-25. Nowhere in the Hayes reference are symptoms defined as lactoferrin concentrations. Furthermore, the Hayes reference fails to teach or suggest comparing the lactoferrin concentration of a first sample with the lactoferrin concentration of a second sample from the same human to determine if the person has had a decrease or increase in

gastrointestinal inflammation. Rather, the Hayes reference makes no comparison of *lactoferrin results* taken at different times from the same individual (mouse). The Office Action dated September 12, 2008, at Page 4, also points out that the Hayes reference does not specifically detect fecal lactoferrin in human patient samples. Likewise, the Sreekant Murthy reference, the Uchida reference, and the Aguila La O reference fail to teach or suggest, nor are these references relied upon for teaching, comparing the lactoferrin concentration of a first sample with the lactoferrin concentration of a second sample from the same human to determine if the person has had a decrease or increase in gastrointestinal inflammation.

Furthermore, it would not be obvious to compare the lactoferrin concentration of a first sample with the lactoferrin concentration of a second sample from the same human to determine if the person has had a decrease or increase in gastrointestinal inflammation in view of the Hayes reference in view of the Sreekant Murthy reference, in further view of the Uchida reference. The invention of claims 1 and 6 is directed to performing a diagnostic test for human IBD. There is a vast difference between human IBD and dextran sulfate inducted ulcerative colitis. First, the Sreekant Murthy reference describes a dextran sulfate model that "resembles" chronic human ulcerative colitis and human colitis-associated colon cancer and can be used in preclinical trials for pharmacological agents. Thus, while the dextran sulfate mouse model may be used for drug discovery, this does not mean it is sensitive enough to be used in diagnostics, especially human diagnostics.

The dextran sulfate model in a mouse is not an adequate model to be used in diagnostics for a variety of reasons. First, according to the Sreekant Murthy reference, the dextran sulfate mouse model "resembles" chronic human ulcerative colitis which is limited to the large bowel. The invention of claims 1 and 6 is directed to both types of IBD, ulcerative colitis

and Crohn's disease. Crohn's disease in humans affects both the small and large bowel. Thus, a dextran sulfate mouse model that only affects the large bowel of a mouse is not sensitive enough to be used for a diagnostic for a human disease that affects both the small and large bowel. Second, Sreekant Murthy teaches away from the use of the dextran sulfate mouse model in human diagnostics as "it is difficult to produce an ideal model of IBD" and "investigators must be careful in interpreting the results" of the model. Clearly, based on the limitations of the dextran sulfate induced mouse model, the mouse model described in Sreekant Murthy is not sensitive enough for use in human diagnostics as the mouse model does not even cover the same portions of the digestive tract and there are vast anatomical differences between mice and humans.

Furthermore, it would not be obvious to compare the lactoferrin concentration of a first sample with the lactoferrin concentration of a second sample from the same human to determine if the person has had a decrease or increase in gastrointestinal inflammation in view of the Hayes reference in view of the Sreekant Murthy reference in further view of the Uchida reference due to the differences between human and mouse feces. Human feces over time varies in consistency and makeup depending on a person's diet and health. It would not have been obvious in view of the combination of references to test the same human for a marker at different times and expect that the concentrations of lactoferrin would allow a determination of a decrease or increase in gastrointestinal inflammation.

First, the Hayes reference does not even teach comparing levels of lactoferrin taken from the same human (or even mouse for that matter) at different times to determine if there has been an increase or decrease in gastrointestinal inflammation. Secondly, it would not be obvious to do so as the Hayes reference dealt with ***mouse*** feces. Laboratory mouse feces

varies greatly from human feces as a laboratory mouse has a consistent diet and other parameters that are controlled by researchers. Unlike mouse feces, human feces can vary greatly in consistency and make-up based on human diet, health, and lifestyle. Fluctuations in fecal antibody levels depend on the consistency of the feces before sample (e.g., whether the feces were initially semi-liquid or liquid form) which confounds attempts to distinguish between disease states even after normalizing sample dilution. Thus, based on the prior art it would not have been obvious to compare lactoferrin concentrations for a human person taken at different times to determine if the person has had a decrease or increase in gastrointestinal inflammation due to the fluctuations in consistency and makeup of human feces.

Furthermore, serum and urine are typically utilized for monitoring the progress of human diseases. Serum and urine have less inherent test variation than that of human feces, and thus it would not be obvious that one could utilize fecal samples taken from the same human at different times to monitor the progression of a disease.

Moreover, the Aguila La O reference does not overcome the above described deficiencies of the cited references. Aguila La O is directed to studying various lactoferrin preparations to allow its use in basic studies, including the diagnosis of gastrointestinal inflammation. *See* Aguila La O reference, Abstract. However, the Aguila La O reference does not teach or suggest comparing the lactoferrin concentration of a first sample with the lactoferrin concentration of a second sample from the same individual to determine if the person has had a decrease or increase in gastrointestinal inflammation.

Claims 1, 2, and 6 are also rejected over the Hayes reference in view of the Sreekant Murthy reference, and in further view of the Sugi reference and the Aguila La O

reference. Applicants respectfully submit that a *prima facie* case of obviousness has clearly not been established for claims 1, 2, and 6.

As discussed above, the Hayes reference, the Sreekant Murthy reference, and the Aguila La O reference fail to teach or suggest comparing the lactoferrin concentration of a first sample with the lactoferrin concentration of a second sample from the same human to determine if the person has had a decrease in gastrointestinal inflammation.

Likewise, as stated in the Office Action, the Sugi reference "does not teach multiple sample collections at different times." *See* Office Action dated 9/12/2008, Page 9. Thus, the Sugi reference does not teach comparing the lactoferrin concentration of a first sample with the lactoferrin concentration of a second sample from the same human to determine if the person has had a decrease in gastrointestinal inflammation. Furthermore, for at least the same reasons stated above, it would not be obvious to compare the lactoferrin concentration of a first sample with the lactoferrin concentration of a second sample from the same human to determine if the person has had a decrease or increase in gastrointestinal inflammation in light of the asserted combination of references.

For at least the reasons stated above, claims 1, 2, and 6 are in condition for allowance. Applicants respectfully request withdrawal of the pending rejections and allowance of claims 1, 2, and 6. It is believed that no fee is due. However, if this belief is in error, the Commissioner is hereby authorized to charge any amount required to Deposit Account No. 19-2112, referencing attorney docket number TLAB.109338.

Respectfully submitted,

Tawni L. Wilhelm
Reg. No. 47,456

TLB/ANLZ

Doc Code: AP.PRE.REQ

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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): TLAB.109338

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Application Number	Filed
10/629,975	07/30/2003

First Named Inventor: BOONE, James Hunter

Art Unit	Examiner
1641	Lisa V. Cook

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- ☐ applicant/inventor.
- ☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- ☑ attorney or agent of record. Registration number 47456.
- ☐ attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

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Signature

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Telephone number

December 12, 2008
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☑ *Total of One forms are submitted.

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
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